Air Pollution and Retained Particles in the Lung

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Epidemiologic evidence associates particulate air pollution with cardiopulmonary morbidity and mortality. The biological mechanisms underlying these associations and the relationship between ambient levels and retained particles in the lung remain uncertain. We examined the parenchymal particle content of 11 autopsy lungs from never-smoking female residents of Mexico City, a region with high ambient particle levels [3-year mean PM_{10} (particulate matter ≤ 10 μm in aerodynamic diameter)= 66 μg/m^3], and 11 control residents of Vancouver, British Columbia, Canada, a region with relatively low levels (3-year mean PM_{10} = 14 μg/m^3). Autopsy lungs were dissolved in bleach and particles were identified and counted by analytical electron microscopy. Total particle concentrations in the Mexico City lungs were significantly higher [geometric mean = 2,055 (geometric SD = 3.9) × 10^6 particles/g dry lung vs. 279 (1.8) × 10^6 particles/g dry lung] than in lungs from Vancouver residents. Lungs from Mexico City contained numerous chain-aggregated masses of ultrafine carbonaceous spheres, some of which contained sulfur, and aggregates of ultrafine aluminum silicate. These aggregates made up an average of 25% of the total particles by count in the lungs from Mexico City, but were only rarely seen in lungs from Vancouver. These observations indicate for the first time that residence in a region with high levels of ambient particles results in pulmonary retention of large quantities of fine and ultrafine particle aggregates, some of which appear to be combustion products. *Key words*: air pollution, environmental exposure, particles, pulmonary retention. *Environ Health Perspect* 109:1039–1043 (2001). [Online 27 September 2001]

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Epidemiologic studies indicate that current levels of particulate air pollution are associated with adverse health outcomes, including increased cardiopulmonary mortality (*1,2*). Although evidence suggests that short-term impacts of particulate air pollution are displacing deaths by more than months, of greater public health significance is the potential for long-term impacts that may shorten lives by years or that may lead to chronic cardiopulmonary morbidity. Several prospective cohort studies provide evidence of such long-term effects, including associations between ambient particles and lung cancer (*3–5*). Whereas acute effects may be limited to those individuals with existing cardiopulmonary disease, chronic exposures may affect a much larger proportion of the exposed population. Although the epidemiologic evidence points to a causal relationship with particles originating in combustion processes, the biological mechanism(s) as well as the exact types and sizes of particles involved are the subjects of intensive investigation. One hypothesis is that the ultrafine particle size fraction is responsible for the epidemiologic observations (*6*). This hypothesis is partly based on the fact that the majority of atmospheric particles, by number, are in the ultrafine mode. These particles, produced in combustion processes, are likely to contain condensates of toxic metals and surface acidity. In animal models, ultrafine particles appear to induce an intense inflammatory reaction and are believed to be translocated to the pulmonary interstitium in large numbers (*7,8*).

Despite the interest in the topic, little is known of the types, sizes, and locations of ambient atmospheric particles in human lungs. Direct measurements of deposited particles in humans are difficult, but animal models show that virtually all types of inhaled particles can be translocated across the alveolar epithelium to the interstitium, from which location they are cleared slowly or not at all (*9*). Analysis of lung parenchymal particle burden can thus provide an indication of the types and numbers of particles to which an individual has been exposed. Also, such analyses can show where potentially toxic particles accumulate. Recently, we used analytical electron microscopy to determine parenchymal particle burden in the lungs of long-term residents of Vancouver who had never smoked tobacco (*10*). Our analysis indicated that 96% of the retained particles were < 2.5 μm in aerodynamic diameter ($PM_{2.5}$), therefore suggesting that epidemiologic investigations should focus on this size class of particles.

In demonstrating biological plausibility it is important to establish a link between ambient concentrations, exposure, and dose. In this study we examined lungs from female, nonsmoking, long-term residents of Mexico City, Mexico, a region with high ambient particle levels, and Vancouver, British Columbia, Canada, a region of much lower levels. In doing so we asked a fundamental question: Does residence in a location with high air pollution levels result in a higher level of biologically delivered dose of pollutants? It is our hypothesis that exposure to high levels of particulate air pollution is reflected in increased interstitial particle burdens. Although this hypothesis may appear simplistic, there has been no direct demonstration that increased ambient particle exposure in fact results in higher particle retention (and, by implication, deposition) in the lung over a lifetime. Such a finding would provide pathologic evidence to support the epidemiologic data associating particulate matter exposure with adverse health outcomes such as mortality. This would provide additional evidence that the observed epidemiologic associations, especially those related to chronic exposures, are in fact biologically plausible. A failure to prove this hypothesis would suggest either that the observed epidemiologic associations may be driven by soluble particles (which would be cleared from the airways and parenchyma) or that the epidemiologic findings are not valid and hence argue against their plausibility.

Materials and Methods

Case selection. The study protocol was reviewed and approved by the University of British Columbia Clinical Research Ethics Board (Approval C96-0511). Lungs for this study were obtained from a general autopsy service at a cardiovascular referral hospital in Mexico City and were compared to lungs obtained from a general hospital autopsy population in Vancouver. To reduce the possibility of occupational dust exposures, only lungs from women were examined. Occupational, smoking, and residential histories were

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obtained by interviews with relatives using a standardized questionnaire. All subjects were lifetime nonsmokers, and none had known occupational dust exposure, including, for the Mexico City lungs, domestic wood smoke exposure. Exposure to environmental tobacco smoke was assessed by evaluation of calcium particles in tissue samples. Retained calcium particles indicate exposure to tobacco smoke (*11*). The lungs from Mexico were collected from women who had been lifetime residents of Mexico City, and the lungs from Vancouver were from residents who had lived in Vancouver for ≥ 20 years. In both locations, inclusion criteria were restricted to cases > 60 years old at time of death. The mean ages were 67 ± 19 (SD) and 64 ± 9 years for Vancouver and Mexico City, respectively. None of the patients had died of lung disease, and the lungs were all morphologically normal except for the presence of minor degrees of pneumonia at autopsy. Four additional cases from Mexico City were examined, but three were excluded because particle levels in the samples were too high to allow for quantitative electron microscopy analysis. An additional sample from Mexico City was excluded because approximately 30% of the particles were determined to contain calcium, an indicator for tobacco smoke exposure (*11*). The total number of retained particles for this case was similar to the other cases from Mexico City. Four additional cases from Vancouver were analyzed, but were excluded from the data analysis because interviews could not be conducted; consequently occupational histories were not obtained. For three of these cases, retained particle concentrations were similar to the other cases from Vancouver, whereas the concentrations from the fourth case, which appeared to be an outlier, were significantly higher.

Tissue dissection and particle counting procedure. All tissues were handled with dust-free gloves. Dissections were performed on formalin-fixed lungs using a dissecting microscope. From each specimen, we selected for analysis a sample of parenchyma weighing 1–2 g from the central portion of the lung, avoiding large airways, and an equivalent size sample that was dried to constant weight to allow expression of results as particles per gram dried tissue. We selected the central tissue sample so that we would analyze comparable tissues from Vancouver and Mexico City cases. Tissue samples were dissolved in bleach and centrifuged at 30,000 × *g* for 20 min; the sediment was washed once to remove the bleach and recentrifuged at 30,000 × *g* for 20 min to ensure that very small particles were not lost during preparation. The preparation was resuspended and collected on 0.1µm filters (Millipore-MF; Millipore Corp., Bedford, MA, USA) and then transferred to coated electron microscope grids (*10*). We previously showed that this approach effectively collects particles of ≥ 0.010 µm (*12*).

For this study, particles larger than 0.010 µm were counted, sized, and identified using an electron microscope (Phillips 400T; Phillips Electronics, Alomelo, The Netherlands) equipped with an energy dispersive X-ray spectrometer (Kevex; Thermo-Kevex X-Ray, Scotts Valley, CA, USA). Approximately 100 particles were counted per sample; particles were measured and identified by a combination of morphology and chemistry as determined by X-ray spectroscopy. For this study particles were characterized as silica, silicates, singlet particles of metals (particles analyzing only as iron,

Table 1. Concentrations of particles (millions of particles per gram of dry tissue) of different types counted in individual samples of lungs from Vancouver residents.

Sample	Silica	Silicate	Metals (single particles)	Carbon Agg	Carbon + sulfur Agg	Kaolin-like Agg	Iron Agg	Misc
42318	67	280	75	ND	ND	ND	ND	8
42313	9	40	16	ND	ND	ND	ND	ND
42324	81	119	46	ND	ND	ND	ND	ND
42304	60	143	56	ND	ND	ND	ND	ND
42329	145	220	95	ND	ND	ND	ND	ND
2458	307	119	72	ND	ND	ND	ND	ND
2459	249	49	16	ND	ND	ND	ND	ND
2460	325	150	40	ND	ND	ND	ND	ND
2461	56	71	62	ND	2	ND	ND	ND
2464	105	139	84	ND	ND	ND	ND	ND
2467	66	88	35	ND	ND	ND	ND	ND
Mean	133	128	54	0	0.2	0	0	0.7
SD	109	7	26	0	0.6	0	0	2.4
Percent of total[a]	37.9	43.0	18.8	0.0	1.0	0.0	0.0	1.9

Abbreviations: Carbon Agg, aggregated particles producing no X-ray peak; Carbon + Sulfur Agg, aggregated particles producing only a sulfur X-ray peak; Iron Agg, aggregated particles analyzing as iron, sometimes with a small silicon peak; Kaolin-like Agg, aggregated particles with a composition similar to kaolinite; Misc, miscellaneous; ND, not detected.
[a]Mean percentage of each type of particle relative to the total number of all types of particles for each case.

Table 2. Concentrations of particles (millions of particles/g dry tissue) of different types counted in individual samples of lungs from Mexico City residents.

Sample	Silica	Silicate	Metals (single particles)	Carbon Agg	Carbon + sulfur Agg	Kaolin-like Agg	Iron Agg	Misc
2416	128	132	48	48	ND	135	10	16
2417	252	1,619	352	100	100	353	ND	ND
2418	217	1,026	116	ND	16	150	251	17
2419	366	230	107	53	32	97	ND	53
2420	192	187	42	16	16	11	37	ND
2423	316	185	86	95	23	24	ND	23
2425	7,262	11,923	2,604	3,776	ND	871	ND	ND
2426	173	236	79	165	52	43	ND	25
2427	770	1,057	258	542	171	199	ND	ND
2428	3,395	8,068	4,243	3,820	1,697	848	ND	212
2448	319	1,033	73	344	25	442	ND	24
Mean	1,217	3,915	1,384	1,537	549	312	132	71
SD	2,215	2,336	728	895	236	288	99	52
Percent of total	24.6	38.2	10.1	10.9	3.2	9.3	2.1	1.6

Abbreviations: Agg, aggregated particles; Misc, miscellaneous; ND, not detected.
[a]Mean percentage of each type of particle relative to the total number of all types of particles for each case.

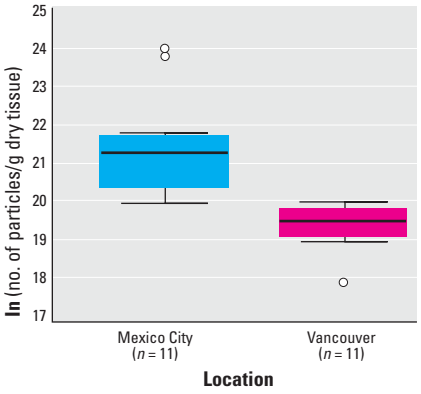

Figure 1. (Ln)Concentration of total particles per gram of dry tissue in Mexico City and Vancouver samples. The top and bottom of boxes indicate the 25th and 75th percentiles, respectively, and the length of boxes is interquartile distance. Upper and lower whiskers extend to the largest and smallest measured values that are 1 interquartile distance from the 75th and 25th percentiles, respectively. Circles are data points that are greater or less than 1 interquartile distance from the 75th or 25th percentiles. The line inside the box indicates the median value.

aluminum, or titanium), and aggregated particles (Tables 1 and 2). With one exception, the aggregated particles were only seen in Mexico City lungs. We classified aggregated particles as follows: *a*) purely carbonaceous if they were composed of more or less spherical particles that produced no X-ray signal [we previously demonstrated our ability to detect purely carbonaceous aggregates by carrying a sample of pure ultrafine carbon black through our preparative procedure, including adding a sample to lung tissue (*12*)]; *b*) carbonaceous + sulfur if they had a similar morphologic appearance but produced a small sulfur peak; *c*) kaolinite-like if they were composed of platy particles with an aluminum:silicon ratio similar to kaolin; and *d*) iron aggregates if they produced X-ray peaks for iron or iron with a small amount of silicon. For purposes of calculating particle numbers and sizes, we treated each aggregate as one particle, but we made additional measurements to determine the sizes of particles that made up the carbonaceous and carbon + sulfur aggregates. Retained particle concentrations were not normally distributed and were therefore log-transformed before all statistical analyses.

Ambient air samples. A limited number of ambient $PM_{2.5}$ particle samples were collected on filters in Mexico City and Vancouver. The purpose of this sampling was to establish whether the types of particles observed in tissue samples were of similar composition and morphology to those found in ambient air. All particle samples were collected by intermittent sampling (1 min of sampling in each 8-min period, for a total of 1,440 min) over a 7-day period in order to provide a sample that was representative of typical particle types. In both locations, samples were collected between October 1999 and January 2000. Particles were collected with Harvard Impactors on polytetrafluoroethylene (Teflon) membrane (Teflo; Pall Life Sciences, Ann Arbor, MI, USA) filters at a flow rate of 4 L/min. In Vancouver, samples were collected at a National Air Pollution Surveillance monitoring site (Kitsilano), and in Mexico City, samples were collected at two sites that are part of the Mexico City ambient monitoring network: one located in the center of the city (Hangares) and another in the southwest (Tlalpan). Three-year average PM_{10} concentrations were 66 μg/m^3 for seven monitoring sites in Mexico City and 14 μg/m^3 from nine sites in Vancouver (*13*).

After sample collection, filters were weighed and then processed for electron microscopy. The filters were wet with 0.1 mL of 95% ethanol, sonicated in 1 mL of distilled, deionized water, centrifuged, and transferred to electron microscope grids following the same procedures used for the tissue samples.

Results

We found significantly higher ($p < 0.001$, *t*-test) concentrations of retained particles in tissue samples from Mexico City than in those from Vancouver (Figure 1, Tables 1 and 2). The geometric mean total particle concentrations in the Mexico City lungs was $2{,}055 \times 10^6$ particles/g dry lung [geometric SD (GSD) = 3.9] as compared to 279 (GSD = 1.8) $\times 10^6$ particles/g dry lung in the Vancouver samples, a nearly 10-fold difference. Examination of individual mineral species showed higher particle concentrations in the Mexico City samples for every particle type examined (compare mean concentrations in Tables 1 and 2).

In addition to the mixture of silicates and other crustal material typically found in tissue samples, the samples from Mexico City contained on average 25.5% aggregated ultrafine particles (Table 2). In particular, we observed chain aggregates of approximately spherical particles that produced no energy dispersive X-ray signal and were, therefore, presumably carbonaceous (Figure 2). Many of these also contained trace amounts of sulfur, which is suggestive of combustion source particles. The morphology of the chain aggregates was remarkably similar to those isolated from Mexico City ambient air samples (Figure 2A) and from diesel exhaust (*14*). In sharp contrast to the Mexico City samples, only 1 aggregate (carbonaceous + sulfur) was detected in the 11 Vancouver tissue samples (Table 1). In Mexico City tissue samples, a large number of aluminum silicate aggregates with a chemical composition similar to kaolinite were also identified, as were occasional aggregates consisting of iron particles that also gave a small X-ray peak for silicon. The origin of these particles was unclear, but they were never observed in Vancouver lungs. On average, the aggregated carbonaceous particles and carbonaceous particles + sulfur made up 14% of the total particles; the kaolinite-like aggregates made up 9%, and the iron aggregates 2% (Table 2). However, if every particle in the aggregates was counted as a single particle, these particles would make up the vast majority of the particles detected in the Mexico City tissue samples.

Tables 3 and 4 show the sizes of particles in the lung tissue samples from the two sites. Overall, the geometric mean particle size in the lungs was similar in both cities, with a mean for all of the cases of 0.35 μm for Mexico City samples and 0.39 μm for Vancouver samples. Table 4 also shows the geometric mean diameters for the aggregated particles detected in lungs from Mexico City. Some of the aggregates were quite large, ranging up to about 4 μm, but most were smaller than 1 μm. Table 5 shows the mean sizes of the particles that made up the carbonaceous and carbon + sulfur aggregates. These were almost all ultrafine particles. The structure of the kaolinite-like aggregates and iron aggregates prevented measurement of individual particle sizes.

Comparison of air samples from the two locations indicated a similar distinction in overall mass (and particle number) concentrations and in composition, with more than 20 times as many aggregates observed in

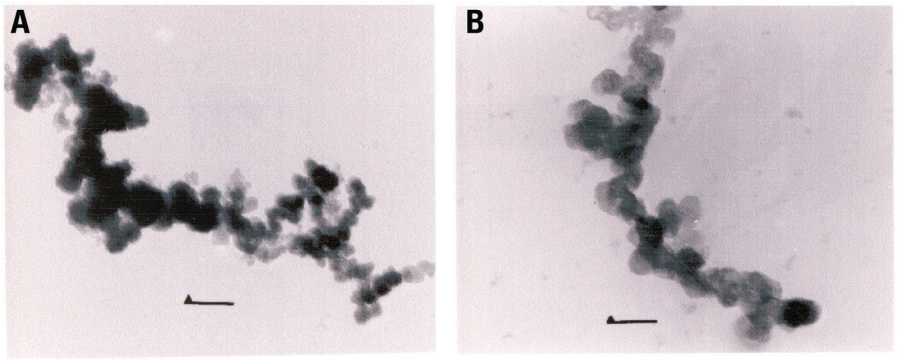

Figure 2. Representative illustration of chained aggregated spherical particles giving no signal (i.e., carbonaceous particles) from (*A*) a Mexico City air sample and (*B*) a Mexico City lung. Bars = 0.1 μm.

Table 3. Geometric mean (GSD) particle diameters (μm) for individual samples of lungs from Vancouver.

Sample	All particles	Carbon + sulfur Agg
42318	0.69 (2.3)	ND
42313	0.69 (2.2)	ND
42324	0.52 (2.2)	ND
42329	0.65 (2.5)	ND
2458	0.31 (2.7)	ND
2459	0.22 (2.3)	ND
2460	0.33 (2.4)	ND
2461	0.31 (2.6)	0.33 (0)[a]
2464	0.31 (2.3)	ND
2467	0.34 (2.3)	ND

ND, not detected. Each aggregate was counted as one particle. No carbon aggregates, kaolin-like aggregates, or iron aggregates were detected in any of the samples from Vancouver.
[a]Only one aggregate identified.

Mexico City samples than in those collected in Vancouver. A more quantitative comparison was not possible because many of the ambient samples collected in Mexico City contained too many aggregates to reliably count. For the limited samples that we collected, the mean $PM_{2.5}$ particle mass concentration measured in Mexico City was 29.5 μg/m^3 (n = 11) compared to a mean concentration of 10.5 μg/m^3 for the samples (n = 6) collected in Vancouver. The geometric mean diameter of ambient carbon aggregates (counting the entire aggregate as one particle) from Mexico City was approximately 1.1 μm, with individual particles within the aggregates in the range of 0.04– 0.15 μm. Because of their complex morphology, it was not possible to determine individual particle sizes for the kaolinite-like aggregates observed in air samples collected in Mexico City.

Discussion

Our observations indicate that long-term residence in an area of high ambient particle concentrations is associated with greater numbers of retained particles in the lung; this shows for the first time that the aggregated ultrafine particles in ambient air can also be found in lung tissue. Our ability to detect retained aggregated ultrafine particles provides evidence that aggregates in air do not disaggregate once they are inhaled, although the sizes in tissue samples were slightly smaller than in air. We cannot determine absolutely if the aggregates we observed in tissue samples are the same as those observed in air samples. However, the similarities between the two (Figure 2) make it unlikely that the aggregates observed in the lungs form after inhalation of airborne ultrafine particles or that they are artifacts of the extraction procedure.

This work, and conclusions that may be drawn from it, is subject to several limitations. In both locations, we observed a large degree of intersubject variability in numbers of retained particles (Figure 1, Tables 1 and 2). This is likely the result of variable exposures as well as interindividual differences in particle clearance and translocation efficiency. Although we have clearly found a difference in the number of retained particles between tissue samples of residents of Vancouver and Mexico City, we were unable to identify differences in the numbers of retained particles in individuals living in higher and lower pollution regions of Mexico City.

Because of the complexity of the analysis and the difficulties in obtaining autopsy samples that meet our inclusion criteria (nonsmoking women > 60 years at death, > 20 year residence in Vancouver or Mexico City, no occupational dust exposure, no deaths from respiratory disease), our sample size was limited and the measured concentrations of retained particles should not be considered quantitatively representative of those for individuals living in Vancouver or Mexico City. However, our analysis shows that the sample size was sufficient to indicate a statistically significant difference between the groups from the two locations. The exclusion of four samples from Mexico City with particle levels that were too high to allow for quantitative electron microscopy analysis does not alter this finding. Had we been able to quantify the high particle levels on these samples, the differences between the two locations would have been even greater.

Our inclusion criteria allowed us to at least partially control for confounding by sex, smoking, age, and duration of residence while we also screened samples for calcium particles as indicators of environmental tobacco smoke exposure. Although we believe that these are the major potential confounding variables of concern for this analysis, it is possible that other unrecognized factors pertaining to differences between the study populations from the two locations contributed to the observed differences.

The number of retained particles we observed is certainly a marked underestimate of the number inhaled because many particles are soluble and therefore would not be detected by our procedures. Further, our analytical approach cannot differentiate between particles originating in airspaces and those that have entered the interstitium, so that we cannot determine what proportion of measured particles have been very recently inhaled. However, our data clearly indicate that, despite exposure to similar types of particles, individuals who reside in an area of high compared to low ambient particle concentrations retain much greater numbers of ambient particles. This finding may seem trivial, but it should be considered in the context of the low mass concentrations of particles in ambient air compared to occupational dust exposures that lead to disease. This finding suggests that even the gravimetrically small particle burden found in regions with high concentrations of ambient particles is able to overwhelm local clearance mechanisms, presumably as a result of particle toxicity.

In conclusion, we observed significantly higher numbers of retained particles in lung tissue samples from long-term residents of Mexico City, a region with high ambient air pollution, relative to samples from long-term residents of Vancouver, a region with much lower ambient pollution levels. Because we restricted our analysis to tissue samples from nonsmoking women, it is likely that the differences observed were due to differences in ambient exposures. Additionally, aggregates of ultrafine particles can be found in large numbers in the lungs of individuals from Mexico City, but were only rarely observed in samples from Vancouver. These particles are morphologically and chemically similar to particles found in ambient air, and at least some of these particles appear to be combustion derived on the basis of morphologic and chemical similarities to particles from motor vehicle exhaust. Our observations demonstrate, therefore, that long-term exposure to ambient particles, and especially to aggregated ambient ultrafine combustion products, results in higher retention of these particles in lung tissue. Because the findings demonstrate

Table 4. Geometric mean (GSD) particle diameters (μm) for individual samples of lungs from Mexico City.

Sample	All particles	Carbon Agg	Carbon + sulfur Agg	Kaolin-like Agg	Iron
2416	0.47 (2.6)	0.40 (2.0)	ND	0.65 (2.3)	0.13 (1.2)
2417	0.39 (2.5)	0.56 (2.1)	0.48 (1.1)	0.52 (1.3)	ND
2418	0.23 (2.5)	ND	0.89 (1.1)	0.78 (2.1)	0.62 (1.7)
2419	0.41 (2.4)	0.44 (1.7)	2.0 (2.8)	0.61 (1.5)	ND
2420	0.37 (2.5)	0.32 (1.5)	0.43 (0)	0.64 (1.8)	0.64 (1.8)
2423	0.38 (2.7)	0.62 (1.6)	1.4 (2.2)	1.29 (1.3)	ND
2425	0.35 (2.8)	0.44 (1.3)	ND	0.38 (2.7)	ND
2426	0.29 (2.3)	0.40 (1.7)	0.48 (1.8)	0.44 (2.1)	ND
2427	0.36 (2.7)	0.30 (1.6)	0.40 (1.7)	0.67 (1.7)	ND
2428	0.25 (2.2)	0.36 (1.4)	0.35 (1.3)	0.52 (1.6)	ND
2448	0.36 (3.4)	0.44 (1.7)	0.31 (3.8)	1.28 (2.6)	ND

ND, not detected. Each aggregate was counted as one particle.

Table 5. Geometric mean (GSD) particle diameters (μm) for individual particles in aggregates in samples of lungs from Mexico City and Vancouver.

Sample	Carbon Agg	Carbon + sulfur Agg
Mexico		
2416	0.073 (1.1)	ND
2417	0.077 (3.6)	0.12 (1.0)
2418	ND	0.25 (1.0)
2419	0.073 (2.9)	0.097 (2.7)
2420	0.054 (1.0)	0.090 (2.5)
2423	0.12 (1.9)	0.17 (1.7)
2425	0.069 (1.7)	ND
2426	0.046 (2.8)	0.075 (2.1)
2427	0.049 (1.9)	0.058 (1.9)
2428	0.027 (1.3)	0.047 (1.9)
2448	0.038 (2.3)	0.019 (1.0)
Vancouver		
2461	ND	0.041 (1.0)[a]

ND, not detected.
[a]Only one aggregate identified.

a link between ambient particle concentrations and a measure of biologically relevant dose, they support the biological plausibility of adverse health effects being associated with exposure to particulate air pollution.

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